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(54) Title: LITHIUM CONTAINING MEDICAMENT FOR COMBATTING PAPILLOMA VIRUS INFECTIONS

(57) Abstract

The invention relates to the use of a physiologically tolerable lithium compound for the manufacture of a medicament for use in combatting human papilloma virus infections.

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LITHIUM CONTAINING MEDICAMENT FOR COMBATTING PAPILLOMA VIRUS INFECTIONS

This invention relates to the use of lithium in the treatment of human papilloma virus (HPV) conditions and in the manufacture of medicaments for use in combatting, ie. treating or preventing, HPV conditions.

Papilloma viruses are DNA viruses that, in humans, cause squamous cell proliferation, ie. the production of wart-like malformations on external and internal body surfaces. These can occur on a variety of surfaces, principally the skin of the limbs and the plantar area, genital skin and mucosa and larynx and oral mucosa.

HPV replication takes place only in fully differentiated keratinocytes, particularly the cells of the upper stratum spinosum and stratum granulosum. Although the viral genome is present in epithelial cells of the basal layer, late gene expression which codes for the proteins of the viral capsid is dependent on differentiation of the squamous epithelial cells, although different HPV types vary in their specificity for different anatomical sites (see Beutner, J. Am. Acad. Dermatol. 20: 114-123 (1989) and Cobb, J. Am. Acad. Dermatol. 22: 547-566 (1990)). Thus for example HPV-1 replicates in the heavily keratinized skin of the palm and sole, HPV-16 replicates preferentially in the genital areas and HPV-11 replicates in the genital and laryngeal epithelium.

HPV papillomas are initially benign but a small percentage can progress to dysplasia or neoplasia under certain circumstances (genetic and environmental) which are not completely understood. There is moreover increasing evidence that, after initial infection, HPV may persist in a latent form and be subsequently reactivated.

HPV infection can generally be diagnosed clinically but infection can be confirmed by laboratory methods including: histology; detection of virus particles by electron microscopy; DNA hybridization on tissue extracts or in situ; and polymerase chain reaction (PCR) amplification of viral DNA fragments.

The time period from acquisition of infection to manifestation of infection can seldom be ascertained but has been estimated at from a few weeks to over a year, eg. 2 years or more. One study of sexual contacts of patients with HPV genital warts indicated an incubation period of three weeks to eight months, averaging 2.8 months (see Oriel, Br. J. Vener. Dis. 47: 1-13 (1971)). Perinatally acquired HPV infection may not manifest itself as genital warts for up to two years and only 57% of cases of HPV laryngeal papilloma in children are diagnosed by two years of age (see Oriel, Br. Med. J. 96: 1484-1485 (1988) and Bennett, Pediatr. Infect. Dis. J. 6: 229-232 (1987)).

HPV can be extremely infectious. In a study of 97 sexual contacts of patients with HPV genital warts, two thirds developed lesions within nine months (see Oriel, Br. J. Vener. Dis. 47: 1-73 (1971)). Studies of male sexual contacts of women with genital HPV disease showed the percentage ultimately diagnosed as infected was higher still - 69% in a study by Sand et al. (Obstet. Gynaecol. 68: 679-681 (1986)) and 88% in a study by Sedlak et al. (Am. J. Gynecol. 154: 494-496 (1986)). It may therefore be concluded that any sexual contact of a patient with genital HPV infection is likely to become infected. The infectivity of other HPV forms seems however to be lower.

HPV infection is spread by direct or indirect contact. Impairment of the epithelial barrier function by trauma

(including mild abrasions), maceration or both greatly predisposes to inoculation of HPV and may be required for infection of fully keratinized skin. Thus plantar HPV warts are commonly acquired from swimming pool or shower-room floors whose rough surfaces abrade moistened keratin from infected feet and help inoculate the virus into the softened skin of others. HPV warts on the other hand may spread widely round the nails or periungual skin in those who bite their finger nails, over habitually sucked fingers in young children, and to the lips and surrounding skin areas in both cases. Shaving may facilitate the spread of HPV infection over the beard area. Occupational handlers of meat, fish and poultry have high incidences of HPV hand warts; this may be attributable to cutaneous injury and prolonged contact with wet flesh and water. Genital warts, as indicated above, have high infectivity. The thinner mucosal surface is presumably more susceptible to HPV viral inoculation than thicker keratinized skin. Moreover lesions have been noted to occur most commonly in both sexes in sites subject to the greatest coital friction (see Oriel, Br. J. Vener. Dis. 47: 1-13 (1971)).

The characteristic histological feature of HPV warts is vacuolation in cells in and below the granular layer, often with basophilic inclusion bodies composed of viral particles and eosinophilic inclusions representing abnormal keratin. Genital HPV warts show extreme acanthosis and papillomatosis, but the horny layer is parakeratoic and not much thickened. There may be many vacuolated cells in the upper Malpighian layer but these may be limited in distribution. The epidermal processes are wide and rounded, with a well defined lower border. The connective tissue is frequently very oedematous and the capillaries tortuous and increased.

The term condyloma acuminatum is frequently used to denote HPV anogenital warts as well as associated HPV type infections in the extragenital sites, eg. the mouth.

HPV anogenital warts are often asymptomatic, but may cause discomfort, discharge and bleeding. The typical anogenital wart is soft, pink, elongated and sometimes filiform or peduculated. The lesions are usually multiple, especially on moist surfaces and their growth may be enhanced during pregnancy or in the presence of other local infections. Large malodorous masses may form on vulvar or perianal skin. This classical "acuminate" (sometimes called papillomatous or hyperplastic) form constitutes about two thirds of anogenital warts. The commonest sites, the areas of frenulum, corona and glans in men, and the posterior introitus in women, correspond to the likely sites of greatest coital friction. Most other lesions are flat and some of these, generally on non-mucosal surfaces such as the penile shaft, pubic skin, perianal skin and groin, are pigmented.

Occasionally vulvar HPV warts are so large in pregnancy as to obstruct vaginal delivery and require Caesarian section.

The duration of anogenital warts varies from a few weeks to many years with recurrences experienced in about 25% of cases at an interval of from 2 months to 23 years. HPV DNA has been found in normal skin adjacent to warts and intrapithelial neoplasia and this latency has been found to correlate well with recurrence after clinical cure (see Ferenczy, New Engl. J. Med. 313: 784-788 (1985)).

HPV infection, like other viral infections, is not

responsive to anti-viral agents in general and a range of different treatments has been developed and are now used. These for the most part depend on local destruction of the infected tissue and not on an anti-viral action. They can be very harsh and locally toxic.

A preparation containing salicylic and lactic acids in a quick drying base (such as collodion/pyroxylin paint or gel) is the treatment of first choice for common and plantar warts.

These preparations however are not suitable for treatment of anogenital warts. Thus they can be particularly irritant on facial skin and other sensitive skin areas. Collodion moreover may cause allergic contact dermatitis.

Podophyllin, a plant-derived resin containing several cytotoxic compounds including podophyllotoxin, has been used in the treatment of anogenital warts as has purified podophyllotoxin. Nonetheless this treatment is problematic. Application of podophyllin to large or bleeding areas has been followed by intra-uterine death, vomiting, diarrhoea, liver damage, renal damage, coma, peripheral neuropathy, bone marrow suppression and death (due to presumed systemic absorption). Oral ingestion has similar effects and can be fatal. In animal studies podophyllin has been found to be an abortifacient.

Podophyllin must therefore not be used on large or bleeding surfaces and its use during pregnancy is generally contra-indicated.

After podophyllin application, some local irritation is expected and, histologically, epidermal intra- and intercellular oedema, mitoses and necrosis are seen.

Podophyllin is generally applied only under professional supervision.

Podophyllin is generally ineffective against warts of other types but has been used in treatment of plantar warts. In this treatment the keratin is pared down, the podophyllin preparation is applied and the wart is then covered by adhesive plaster. The dressing is removed after about one week and the treatment is repeated if the wart persists. Acute pain may occur, due to formation of a sterile abscess.

An alternative approach is cryotherapy. In hospital practice, liquid nitrogen is commonly used for this. The main disadvantage of this technique however is pain. This can be unpredictable and surprisingly variable between patients, but in some cases, especially with longer freezing times, the pain may be severe and persist for many hours or even a few days. Occasionally freezing may cause damage to underlying tissues and depigmentation may occur. Depigmentation may of course be a significant cosmetic disadvantage to certain patients. In areas of sensitive skin, eg. in the genital area, cryotherapy is not a preferred technique.

Surgical excision (and analogous techniques such as curettage and electrocoagulation) of HPV warts is also possible although it is generally to be avoided since scarring is inevitable and recurrences of the wart in the scar are frequent. Again, in areas of sensitive skin such techniques are preferably avoided.

Cytotoxic agents, such as bleomycin, have been used to combat HPV warts, generally by injection directly into the lesion by a physician. Injections are painful and local anaesthesia may be required for sensitive sites.

Various interferons have been tried in attempts to deal with refractory warts. However the results are not always conclusive. In one study, of 28 patients with refractory anogenital warts given intramuscular human gamma-interferon only two were cleared with thirteen showing some improvement.

A further known treatment for HPV infection is topical application of 5-fluorouracil. If used periungually however, 5-fluorouracil may cause onycholysis and topical application of 5-fluorouracil ointment has resulted in a high incidence of hyperpigmentation as well as erythema and erosion.

There is thus a need for a simple safe and effective means of treating HPV infection, in particular of sensitive skin areas and of HPV anogenital warts.

It has now surprisingly been found that lithium therapy is effective in this regard.

Thus viewed from one aspect the invention provides the use of a physiologically tolerable lithium compound (eg. a lithium salt which acts as a source of bioavailable lithium ions and has a physiologically tolerable counterion) for the manufacture of a medicament for use in combatting human papilloma virus infections, particularly anogenital warts.

Viewed from a further aspect the invention provides a method of treatment of a human subject to combat human papilloma virus infection, said method comprising administering to said subject (eg. a person infected with HPV or at risk of HPV infection due to exposure to HPV infected individuals, for example as a result of sexual contact, birth or repeated exposure to environments where HPV transmission is frequent (such as

communal swimming pools, changing rooms and the like)) an effective amount of a physiologically tolerable lithium compound.

While lithium is known to be effective in the treatment of depression, alcoholism, herpes infections, and seborrhoeic dermatitis, its utility in the treatment of HPV disease is surprising and hitherto has not been suggested. Other agents effective in treating herpes infections, such as acyclovir, are ineffective in treating HPV infections. Orally administered lithium moreover is widely acknowledged to have toxic side effects and the margin between therapeutic efficacy and toxicity for its major indication (treatment of manic depressive illness) is narrow. Accordingly in the absence of a strong positive indication of a beneficial activity against a given condition, lithium is not a drug which would routinely be administered.

Lithium thus was not an obvious candidate in the search for a treatment for HPV infection. Its efficacy is unpredictable and surprising since a positive effect on one viral infection cannot readily be extrapolated to a prediction of a similar effect on another, as noted for acyclovir above.

Lithium may be administered according to the invention in any form which will effectively deliver it to the infected area, although inorganic and organic salts are generally preferred. Suitable examples of organic and inorganic salts include lithium succinate, lithium chloride, lithium carbonate and lithium orotate, lithium succinate being generally preferred.

It may also be useful in certain circumstances to administer the lithium in the form of a salt with a polyunsaturated fatty acid, preferably a C_{18-22}

polyunsaturated fatty acid such as gammalinolenic or dihomogammalinolenic acid. This has the benefit that, being in a form which is both water and lipid soluble, the lithium is more effectively delivered across cell membranes, and at the same time can be easily formulated into aqueous-based non-greasy compositions.

Lithium is generally employed according to the present invention in any pharmaceutical formulation suitable for topical administration although, less preferably, other administration routes (eg. oral, rectal and parenteral, for example by injection into the vasculature or subcutaneous injection) may be used. Thus for example, topical pharmaceutical compositions for use according to the present invention may be formulated in conventional manner as ointments, creams, lotions, gels, sprays, salves, sticks, soaps or any other appropriate vehicles. Since the therapeutically effective component, the lithium ions, are charged, it is also possible to deliver lithium transdermally by electrophoresis. The chosen lithium compound may be incorporated, optionally together with other active substances, with one or more conventional carriers, excipients or formulation aids, eg. silica and DLMG. Suitable compositions include, for example, those disclosed in EP-A-289204 (Efamol).

Viewed from a further aspect the invention thus provides a pharmaceutical composition for use in combatting a human papilloma virus infection, said composition comprising a physiologically tolerable lithium compound together with at least one pharmaceutical carrier or excipient.

Where the lesion being treated is in a keratinized area, benefits in lithium delivery may also be obtained by formulating the lithium with a skin penetration-assisting or keratolytic agent to aid transdermal

passage of the lithium. Suitable keratolytic agents may be basic or acidic and include urea and salicylic acid. Suitable skin penetration-assisting agents include dimethylsulphacetamide or more preferably dimethylsulphoxide (DMSO).

The precise concentrations of lithium in the topical compositions of the invention will depend of course on a number of factors including, for example, the severity of the condition to be treated, the form of lithium used and the physical nature of the pharmaceutical composition. Generally, however, an effective lithium concentration in the composition is 0.001 to 10% by weight lithium ion, preferably 0.005 to 5%, and most especially preferably 0.3 to 2%. Thus for example where the active agent is lithium succinate, topical compositions may contain 1 to 20% by weight, preferably 4 to 12% and especially 5 to 9% of the lithium compound.

Treatment duration will generally be for a period of weeks, e.g. 1 to 14 weeks, e.g. 10 days to 12 weeks, preferably 2 to 10 weeks, more preferably about 8 weeks or less, for example 3 to 5 weeks.

The invention will now be described with reference to the following non-limiting Examples in which all percentage, parts and ratios are by weight unless otherwise specified:

EXAMPLES

EXAMPLE 1

Pharmaceutical Composition

An ointment was prepared with the following composition:

	% wt/wt
Lithium succinate	8.0
Zinc sulphate	0.05
Wool alcohols BP	3.3
Hard paraffin BP	13.2
White soft paraffin BP	5.4
Liquid paraffin	33.0
Citric acid monohydrate	q.s.
Deionised water	37.05

The ointment was packaged in 20g tubes.

EXAMPLE 2

Pharmaceutical Composition

A cream was prepared with the following composition:

	% wt/wt
Lithium succinate	8.0
Zinc sulphate heptahydrate	0.05
Propylene glycol	2.0
Syncrowax BB4	6.0
Imwitor 370	4.0
Isopropyl myristate	6.0
Stearic acid	3.0
Myrj 52F	2.0
Sorbitan monolaurate	1.0
Poloxamer 188	1.0
Triethanolamine	0.5
Citric acid monohydrate	q.s.
Deionised water	65.45

The cream was packaged in 20g tubes.

EXAMPLE 3

Pharmaceutical Composition

A lotion was prepared with the following composition:

	% wt/wt
Lithium succinate	6.0
Isopropyl alcohol	30.0
Glycerol	5.0
Hydroxyethyl cellulose	0.375
Citric acid (30% w/v aq.sol)*	qs to pH 6.5 to 7.5
Purified water	qs to 100.00 ml

*Citric acid 30% w/v aqueous solution is made up from Citric Acid Monohydrate EP (1986) and Purified Water EP (1990).

The lithium succinate is dissolved in a portion of the purified water. The pH is adjusted to pH 6.5 - 7.5 with 30% w/v citric acid solution. The hydroxyethyl cellulose is dispersed in a portion of the isopropyl alcohol and added to a portion of the purified water with stirring to dissolve. The hydroxyethyl cellulose solution, glycerol, and remaining isopropyl alcohol is added to the lithium succinate solution with stirring. The lotion is made to volume with purified water and is filled into its final containers.

EXAMPLE 4

Pharmaceutical Composition

A shampoo was prepared with the following composition:

	% wt/wt
Lithium succinate	8.0
Sodium lauryl sulphate (28%)	37.0

Sodium N-lauroyl sarcosinate (30%)	17.5
Coconut diethanolamide	4.0
Polyethoxylated glyceryl cocoate	2.0
Quaternised hydrolysed collagen protein	1.0
Imidurea	0.2
Mixed paraben esters	0.3
Citric acid monohydrate	qs to pH 6.5 to 8.0
Deionised water	qs to 100.0

The lithium succinate is dissolved in water and the pH is adjusted to 6.5-8.0 with citric acid. The remaining ingredients are mixed together and the lithium succinate solution is added. The shampoo is mixed until all the ingredients have dissolved and the bulk is homogeneous. The pH is checked and if necessary, adjusted to 6.5-8.0 with citric acid solution (30%). The bulk is made up to weight with water and left to stand for some hours to allow deaeration, before storage or filling into the final containers.

Similar formulations to the ones above can be made with other lithium derivatives, including lithium salts of polyunsaturated fatty acids.

EXAMPLE 5

Double blind parallel trial in treatment of anogenital warts

An equal randomisation plan was applied separately to each individual sex group of 101 patients. Of the patients who entered the trial, 51 were allocated to the Active treatment group and 50 to the Placebo group. Within the Active group 21 patients were Female and 30 were Male. The Placebo group also consisted of 21 Females, and 29 Males. In total there were 42 Females and 59 Males.

The selection criterion for the study population was either Males or Females aged 18 and over with clinically diagnosed external Condyloma Acuminatum (Anogenital Warts), who had not yet received any treatment for the infection. Patients with internal lesions or any concurrent untreated sexually transmitted disease were excluded. Exemption was also given to patients with any other concurrent medical conditions, such as, cardiovascular or renal disease, hypothyroidism, Addison's disease, sodium depletion or conditions requiring low salt intake. In addition, patients on treatment for diuretics or immunodeficiency disease were excluded.

Each patient was given a baseline assessment for each area of the body covered with lesions. The infected areas for both sexes were Perianal, Anal and Uretheral. In addition, Penal and Scrotal for Males, and Cervical, Vulval and Vaginal for Females, were also assessed. The investigator recorded, for each area, the Total Area Covered by lesions (mm^2). Patients' infection was assessed at baseline (week 0), before being randomly assigned to a treatment group. They were then asked to apply the treatment 4 times daily for a period of 1 month. The follow up period was a further optional 8 weeks of assessment without treatment. The assessments both, clinical and self-reported were recorded at weeks 2 and 4, 6, 8 and 12. A single investigator at the centre examined each patient and made all consecutive assessments throughout the trial. The statistical analysis focused on the assessment within the treatment period (0-4 weeks).

The Active treatment involved use of a cream containing 8% lithium succinate and 0.05% zinc sulphate as described in Example 2. The Placebo is a standard cream base containing 0.1% Euxyl K100 on a preservative. The

creams were applied topically to the affected sites four times daily.

The variables listed below were estimated using the Total Area Covered by Lesions (mm^2):

1. Overall Coverage of Lesions Across All Areas (mm^2) (OCL).

2. Percentage Change of Overall Coverage of Lesions from Baseline ie. {(Week 4 ÷ Baseline) - 1} x 100%

The primary statistical analysis was based on only 2 out of 3 time points in the treatment period, ie. baseline (week 0), and end of treatment (week 4). The Overall Coverage of Lesions (mm^2), was estimated by summing the Total Area Covered by Lesions (mm^2) for every area at each separate time point for each patient.

The primary efficacy variable was the Percentage Change from Baseline of the Overall Coverage of Lesions. Over all patients, the Active treatment produced a significant reduction of 42% in the Overall Coverage of lesions, compared with the Placebo (p-value = 0.013). Moreover, for Males the Active treatment produced a significant reduction of 65% compared with the Placebo group (p-value = 0.017).

Claims

1. The use of a physiologically tolerable lithium compound for the manufacture of a medicament for use in combatting human papilloma virus infections.

2. Use as claimed in claim 1 of a lithium salt having a physiologically tolerable counterion.

3. Use as claimed in claim 2 of a lithium salt selected from lithium succinate, lithium chloride, lithium carbonate and lithium orotate.

4. Use as claimed in any one of claims 1 to 3 for the manufacture of a medicament for use in combatting anogenital warts.

5. A method of treatment of a human subject to combat human papilloma virus infection, said method comprising administering to said subject an effective amount of a physiologically tolerable lithium compound.

6. A method as claimed in claim 5 wherein said lithium compound is applied topically to an HPV infected or at-risk surface.

7. A method as claimed in either of claims 5 and 6 wherein said lithium compound is administered repeatedly over a period of 2 to 10 weeks.

8. A method as claimed in any one of claims 5 to 7 wherein said lithium compound is a lithium salt having a physiologically tolerable counterion.

9. A method as claimed in claim 8 wherein said lithium salt is selected from lithium succinate, lithium chloride, lithium carbonate and lithium orotate.

10. A method as claimed in any one of claims 5 to 9 for the treatment of a human infected with a human papilloma virus infection.

11. A method of treatment as claimed in claim 10 wherein said human has anogenital warts.

12. A pharmaceutical composition for use in combatting a human papilloma virus infection, said composition comprising a physiologically tolerable lithium compound together with at least one pharmaceutical carrier or excipient.

INTERNATIONAL SEARCH REPORT

Interna nal Application No
PCT/GB 97/02985

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K33/00 A61K31/19

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 289 284 A (EFAMOL HOLDINGS) 2 November 1988 see page 6, line 39-43	1,2,5
A	see claims	3,4,6-12
X,P	WARD KA ET AL: "A pilot study to investigate the treatment of anogenital warts with Topical Lithium Succinate cream (8% lithium succinate, 0.05% zinc sulphate)." INT J STD AIDS, AUG 1997, 8 (8) P515-7, ENGLAND, XP002052990 see abstract	1-12

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[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

2

Date of the actual completion of the international search	Date of mailing of the international search report
22 January 1998	27.02.98

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Leherte, C

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int ational application No.
PCT/GB 97/02905

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 5-11
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 5-11 are directed to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

information on patent family members

Inter nal Application No
PCT/GB 97/02905

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0289204 A	02-11-88	AU 618738 B	09-01-92
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